

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE  
in its capacity as elected Office

Date of mailing (day/month/year) 27 July 2001 (27.07.01)	
International application No. PCT/US00/30294	Applicant's or agent's file reference P1735R1
International filing date (day/month/year) 02 November 2000 (02.11.00)	Priority date (day/month/year) 02 November 1999 (02.11.99)
Applicant SHEN, Ben-Quan et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

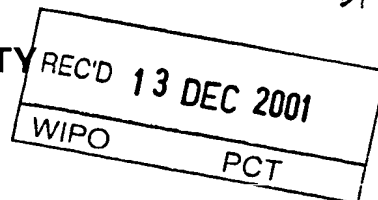
23 May 2001 (23.05.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Antonia Muller
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference JEC/FP5931043	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/30294	International filing date (day/month/year) 02/11/2000	Priority date (day/month/year) 02/11/1999
International Patent Classification (IPC) or national classification and IPC A61K38/18		
Applicant GENENTECH, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  23/05/2001	Date of completion of this report  10.12.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer  Siatou, E  Telephone No. +49 30 25901 327 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/30294

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

**Description, pages:**

1-45 as originally filed

**Claims, No.:**

1-20 as originally filed

**Drawings, sheets:**

1/20-20/20 as originally filed

**Sequence listing part of the description, pages:**

1-3, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☒ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/30294

- ☐ the description,      pages:
- ☐ the claims,      Nos.:
- ☐ the drawings,      sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-13 as well as 14-20 (partially) in respect of industrial applicability.

because:

- ☒ the said international application, or the said claims Nos. 1-13 as well as 14-20 (partially) in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-2, 8-14 .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/30294

**citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	6-7, 16-17
	No:	Claims	1-5, 8-15, 18, 20
Inventive step (IS)	Yes:	Claims	6-7, 16-17
	No:	Claims	1-5, 8-15, 18, 20
Industrial applicability (IA)	Yes:	Claims	14-20 partially
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/30294

**Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-13 and 14-20, only as far as in vivo application is concerned, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. No opinion will be given for those parts of the application which have not been the subject of a search report.

Moreover, and as already stated in the search phase, support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT is to be found for only a very small number of compounds within the scope of the present application, namely the compounds disclosed in dependent claims 3-7 and 15-20 of the present application.

**Re Item V**

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The Applicant's attention is drawn to the fact that the present opinion expressed as to the novelty, inventive step and industrial applicability refers only to the matter for which an international search report has been drawn up.

Reference is made to the following documents:

D1: WO-A-9820027

D2: WO-A-9816551

D3: WO-A-9708313

D4: US-A-5955311

D5: European Heart Journal, vol. 18, Suppl., 24 Aug. 1997, p. 4 (& I. Zachary et al)

D6: Human Gene Therapy, vol. 8(15), 10 Oct. 1997, pp. 1737-44 (& M. Laitinen et al)

D1 discloses compositions containing vascular endothelial growth factor (VEGF) or VEGF receptor agonists for treating NO-linked conditions, such as intimal hyperplasia, hypertension or atherosclerosis (see claims 1-7, 14-15, page 6, lines 4-10 and page 10,

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/30294

line 25- page 11, line 29). The subject matter of claims 1-5, 8, 10-15 and 20 of the present application does not meet the requirements of Art. 33(2) and 33(3) PCT.

D2 and D3 also discloses compositions containing VEGF variants for treating diseases characterised by undesirable vascularization, such as atherosclerosis (see D2 claims 1-15 and page 5, line 23 and D3 claims 1-32 and page 35, lines 2-12). The subject matter of claims 1-2, 4, 8-15 and 18 does not meet the requirements of Art. 33(2) and 33(3) PCT.

D4 discloses compositions containing monoclonal antibodies against the VEGF receptor and their use in treating neoplastic and non-neoplastic conditions characterised by excessive angiogenesis (see column 6, line 11-column 7, line 36). The subject matter of claims 1 and 4-8 does not meet the requirements of Art. 33(2) and 33(3) PCT.

D5 (see abstract) and D6 (see abstract and page 1743, left column) disclose that VEGF stimulates NO production and suggests that administration of VEGF or VEGF transfer may be used for treating vascular smooth muscle cell proliferation associated with restenosis. The subject matter of claims 1-3 and 8-13 does not meet the requirements of Art. 33(2) and 33(3) PCT.

**Re Item VI**

Certain documents cited

Certain published documents (Rule 70.10)

Application No

Patent No      Publication date

(day/month/year)      Filing date

(day/month/year)      Priority date (valid claim)

(day/month/year)

WO-A-0071713	30.11.00	18.05.00	20.05.99
WO-A-0063380	26.10.00	10.04.00	16.04.99

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/30294

WO-A-0013702	16.03.00	09.09.99	23.02.99
			09.09.98
			26.03.99
			27.03.99

**Re Item VIII**

Certain observations on the international application

Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. No technical characteristics are given for the VEGF receptor agonist. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.



# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>P1735R1</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 30294</b>	International filing date (day/month/year) <b>02/11/2000</b>	(Earliest) Priority Date (day/month/year) <b>02/11/1999</b>
Applicant  <b>GENENTECH, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1B

☐ None of the figures.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1-2, 8-14 relate to an extremely large number of possible compounds acting as VEGF receptor agonists. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the use of compounds as disclosed in claims 3-7 and 15-20 of the present application,

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/30294

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/18 A61P9/04 A61P9/10 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, MEDLINE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 71713 A (SCIOS INC.) 30 November 2000 (2000-11-30) claims 1-42 ---	1-3,8-15
P,X	WO 00 63380 A (GENENTECH INC.) 26 October 2000 (2000-10-26) claims 1-19 page 5, line 42 - line 45 ---	1
P,X	WO 00 13702 A (SCIOS INC.) 16 March 2000 (2000-03-16) claims 1-42 ---	1-3,8-15
X	WO 98 20027 A (EUROGENE LIMITED) 14 May 1998 (1998-05-14) claims 1-7,14,15 page 10, line 25 -page 11, line 29 --- -/--	1-5,8, 10-15,20



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

7 August 2001

Date of mailing of the international search report

16/08/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Siatou, E

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/30294

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 16551 A (GENENTECH) 23 April 1998 (1998-04-23) claims 1-15 page 5, line 23 ----	1,2,4,8, 10-14
X	WO 97 08313 A (GENEHECH) 6 March 1997 (1997-03-06) claims 1-32 page 35, line 2 - line 12 ----	1,2,4, 8-15,18
X	US 5 955 311 A (P. ROCKWELL ET AL) 21 September 1999 (1999-09-21) column 6, line 11 -column 7, line 36 ----	1,4-8
X	ZACHARY I ET AL: "VASCULAR ENDOTHELIAL GROWTH FACTOR STIMULATES NITRIC OXIDE PRODUCTION AND PROSTACYCLIN SYNTHESIS IN HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS" EUROPEAN HEART JOURNAL, THE EUROPEAN SOCIETY OF CARDIOLOGY, XX, vol. 18, no. SUPPL, 24 August 1997 (1997-08-24), page 4 XP002072658 ISSN: 0195-668X abstract ----	1-3,8-13
X	LAITINEN M ET AL: "VEGF GENE TRANSFER REDUCES INTIMAL THICKENING VIA INCREASED PRODUCTION OF NITRIC OXIDE IN CAROTID ARTERIES" HUMAN GENE THERAPY, XX, XX, vol. 8, no. 15, 10 October 1997 (1997-10-10), pages 1737-1744, XP002072657 ISSN: 1043-0342 abstract ----	1,3,8, 11-13
X	HARADA K ET AL: "VASCULAR ENDOTHELIAL GROWTH FACTOR ADMINISTRATION IN CHRONIC MYOCARDIAL ISCHEMIA" AMERICAN JOURNAL OF PHYSIOLOGY: HEART AND CIRCULATORY PHYSIOLOGY, THE AMERICAN PHYSIOLOGICAL SOCIETY, XX, vol. 270, no. 5, PART 2, May 1996 (1996-05), pages H1791-H1802, XP000946368 ISSN: 0363-6135 abstract ----- -/--	1-3,11

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/30294

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MORBIDELLI L ET AL: "NITRIC OXIDE MEDIATES MITOGENIC EFFECT OF VEGF ON CORONARY VENULAR ENDOTHELIUM" AMERICAN JOURNAL OF PHYSIOLOGY: HEART AND CIRCULATORY PHYSIOLOGY, THE AMERICAN PHYSIOLOGICAL SOCIETY, XX, vol. 270, no. 1, PART 2, 1996, pages H411-H415, XP002072656 ISSN: 0363-6135 abstract</p> <p>-----</p>	1-20

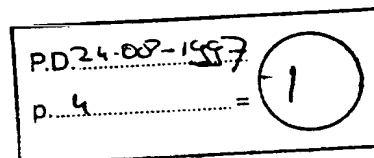
## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/30294

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0071713 A	30-11-2000	AU 5023300 A AU 5026100 A WO 0071716 A	12-12-2000 12-12-2000 30-11-2000
WO 0063380 A	26-10-2000	AU 4222000 A	02-11-2000
WO 0013702 A	16-03-2000	AU 5910599 A AU 6028599 A BR 9913533 A BR 9913564 A EP 1112083 A EP 1109571 A WO 0013703 A	27-03-2000 27-03-2000 05-06-2001 22-05-2001 04-07-2001 27-06-2001 16-03-2000
WO 9820027 A	14-05-1998	AU 729420 B AU 4790697 A EP 0941116 A NO 992106 A PL 333272 A	01-02-2001 29-05-1998 15-09-1999 30-06-1999 22-11-1999
WO 9816551 A	23-04-1998	AU 718327 B AU 5152398 A EP 0931092 A JP 2000507456 T	13-04-2000 11-05-1998 28-07-1999 20-06-2000
WO 9708313 A	06-03-1997	US 6020473 A AU 6857296 A EP 0851920 A JP 10511557 T US 6057428 A	01-02-2000 19-03-1997 08-07-1998 10-11-1998 02-05-2000
US 5955311 A	21-09-1999	US 5861499 A US 5840301 A US 5874542 A AU 1914795 A CA 2185683 A EP 0741748 A WO 9521868 A	19-01-1999 24-11-1998 23-02-1999 29-08-1995 17-08-1995 13-11-1996 17-08-1995



**148 Vascular endothelial growth factor stimulates nitric oxide production and prostacyclin synthesis in human umbilical vein endothelial cells**

I. Zachary, C. Wheeler-Jones<sup>1</sup>, H. Abedi, J.F. Martin. *Cruciform Project and Department of Medicine, Rayne Institute, University College, London, UK, 5 University Street, London WC1E 6JJ, UK, <sup>1</sup> Vascular Biology Research Centre, King's College London, Campden Hill Road Kemsington, London W8 7AH, UK*

Recent findings suggest that VEGF, a specific endothelial cell mitogen and potent angiogenic factor, may reduce neo-intima formation in the rat carotid balloon injury model of restenosis. The mechanism(s) involved are, however, unclear. We have shown that VEGF production by vascular smooth muscle cells (VSMC) is induced by hypoxia, growth factors and cytokines. This prompted us to examine whether VEGF could induce the production by endothelial cells of factors which could in turn exert paracrine inhibitory effects on VSMC proliferation. Treatment of human umbilical vein endothelial cells with VEGF induced the rapid and concentration-dependent formation of nitrite, a measure of nitric oxide (NO) synthesis via the endothelial NO synthase. In 10 independent experiments, the maximum mean stimulated rate of nitrite formation was approximately 1 nmol/10<sup>6</sup> cells/min (n = 10). In addition, our results also showed that VEGF induced a striking concentration-dependent increase in production of the prostacyclin PGI<sub>2</sub> as determined by radioimmunoassay of 6-keto PGF<sub>1α</sub>, the stable breakdown product of PGI<sub>2</sub>. Cultured HUVECs constitutively produced TGF-β<sub>1</sub>, but VEGF had no apparent effect on production of active TGF-β<sub>1</sub>. Since NO and prostacyclins are both potent inhibitors of VSMC proliferation in vitro, these findings suggest that VEGF can potentially regulate VSMC proliferation in arteries indirectly by stimulating the production of endothelium-derived inhibitory factors. These results support the hypothesis that VEGF may function as a homeostatic factor in adult blood vessels contributing to the regulation of VSMC proliferation and suggest a completely novel mechanism of action for this important cytokine. These results further suggest that administration of VEGF or VEGF gene transfer may offer a novel therapeutic strategy for the inhibition of VSMC proliferation associated with neo-intima formation in restenosis and stenosis following either angioplasty or arterial bypass surgery.

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## PCT REQUEST

P1735R1

Original (for SUBMISSION) - printed on 02.11.2000 10:21:25 AM

0 0-1	For receiving Office use only International Application No.	PCT/US 00/30294
0-2	International Filing Date	RO/US 02 NOV 2000 (02.11.00)
0-3	Name of receiving Office and "PCT International Application"	PCT INTERNATIONAL APPLICATION RO/US
0-4 0-4-1	Form - PCT/RO/101 PCT Request Prepared using	PCT-EASY Version 2.91 (updated 10.10.2000)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	P1735R1
I	Title of invention	MODULATION OF eNOS ACTIVITY AND THERAPEUTIC USES THEREOF
II II-1 II-2 II-4 II-5	Applicant This person is: Applicant for Name Address:	applicant only all designated States except US GENENTECH, INC. 1 DNA Way South San Francisco, CA 94080-4990 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	650-225-1000
II-9	Facsimile No.	650-952-9881
III-1 III-1-1 III-1-2 III-1-4 III-1-5	Applicant and/or inventor This person is: Applicant for Name (LAST, First) Address:	applicant and inventor US only SHEN, Ben-Quan 2055 32nd Avenue San Francisco, CA 94116 United States of America
III-1-6	State of nationality	CN
III-1-7	State of residence	US



## PCT REQUEST

P1735R1

Original (for SUBMISSION) - printed on 02.11.2000 10:21:25 AM

III-2	<b>Applicant and/or inventor</b>	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ZIONCHECK, Thomas
III-2-5	Address:	P. O. Box 370153 Montara, CA 94037 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
IV-1	<b>Agent or common representative; or address for correspondence</b>	
	The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	CUI, Steven X.
IV-1-2	Address:	GENENTECH, INC. 1 DNA Way South San Francisco, CA 94080-4990 United States of America
IV-1-3	Telephone No.	650-225-1000
IV-1-4	Facsimile No.	650-952-9881
IV-2	<b>Additional agent(s)</b>	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	AGARWAL, Atulya R.; BARNES, Elizabeth M.; CARPENTER, David A.; CONLEY, Deirdre L.; EVANS, David W.; JOHNSTON, Sean A.; KLEID, Dennis G.; KUBINEC, Jeffrey S.; LEE, Wendy M.; LOVE, Richard B.; SCHWARTZ, Timothy R.; SVOBODA, Craig G.; TAN, Lee K.
V	<b>Designation of States</b>	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT

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V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW	
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	02 November 1999 (02.11.1999)	
VI-1-2	Number	60/163,132	
VI-1-3	Country	US	
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description (excluding sequence listing part)	45	-
VIII-3	Claims	2	-
VIII-4	Abstract	1	p1735r1.txt
VIII-5	Drawings	20	-
VIII-6	Sequence listing part of description	3	-
VIII-7	TOTAL	75	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-15	Nucleotide and/or amino acid sequence listing in computer readable form		separate diskette
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	Figure of the drawings which should accompany the abstract	1B	
VIII-19	Language of filing of the international application	English	

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IX-1	Signature of applicant or agent	
IX-1-1	Name (LAST, First)	CUI, Steven X.

## FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	527 Rec'd PCT/PTC 02 NOV 2000
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

## FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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**PCT (ANNEX - FEE CALCULATION SHEET)**Original (for **SUBMISSION**) - printed on 02.11.2000 10:21:25 AM

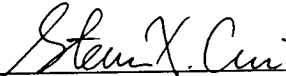
(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only			
0-1	International Application No.	<b>PCT/US 00/30294</b>		
0-2	Date stamp of the receiving Office	<b>RO/US 02 NOV 2000 (02.11.00)</b>		
0-4	Form - PCT/RO/101 (Annex)			
0-4-1	PCT Fee Calculation Sheet Prepared using	<b>PCT-EASY Version 2.91 (updated 10.10.2000)</b>		
0-9	Applicant's or agent's file reference	<b>P1735R1</b>		
2	Applicant	<b>GENENTECH, INC., et al.</b>		
12	Calculation of prescribed fees	fee amount/multiplier	total amounts (USD)	
12-1	Transmittal fee T	⇒	<b>240</b>	
12-2	Search fee S	⇒	<b>846</b>	
12-3	International fee			
	Basic fee (first 30 sheets) b1	<b>427</b>		
12-4	Remaining sheets	<b>45</b>		
12-5	Additional amount (X)	<b>10</b>		
12-6	Total additional amount b2	<b>450</b>		
12-7	b1 + b2 = B	<b>877</b>		
12-8	Designation fees			
	Number of designations contained in international application	<b>87</b>		
12-9	Number of designation fees payable (maximum 8)	<b>8</b>		
12-10	Amount of designation fee (X)	<b>92</b>		
12-11	Total designation fees D	<b>736</b>		
12-12	PCT-EASY fee reduction R	<b>-132</b>		
12-13	Total International fee (B+D-R) I	⇒	<b>1,481</b>	
12-14	Fee for priority document			
	Number of priority documents requested	<b>1</b>		
12-15	Fee per document (X)	<b>15</b>		
12-16	Total priority document fee P	⇒	<b>15</b>	
12-17	<b>TOTAL FEES PAYABLE (T+S+I+P)</b>	⇒	<b>2,582</b>	
12-19	Mode of payment	<b>authorization to charge deposit account</b>		
12-20	Deposit account instructions The receiving Office:	<b>United States Patent and Trademark Office (USPTO) (RO/US)</b>		
12-20-1	is hereby authorized to charge the total fees indicated above to my deposit account	✓		
12-20-2	is hereby authorized to charge any deficiency or credit any over-payment in the total fees indicated above to my deposit account	✓		
12-21	Deposit account No.	<b>07-0630</b>		
12-22	Date	<b>02 November 2000 (02.11.2000)</b>		

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P1735R1

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12-23	Name and signature	CUI, Steven X. 
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## VALIDATION LOG AND REMARKS

13-2-1	Validation messages Request	Green? The title of the invention should preferably be entered in capital letters. Please verify.
13-2-3	Validation messages Names	Green? Agent 1.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 2.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 3.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 4.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 5.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 6.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.
		Green? Agent 7.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.

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		<p>Green?</p> <p>Agent 8.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.</p>
		<p>Green?</p> <p>Agent 9.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.</p>
		<p>Green?</p> <p>Agent 10.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.</p>
		<p>Green?</p> <p>Agent 11.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.</p>
		<p>Green?</p> <p>Agent 12.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.</p>
		<p>Green?</p> <p>Agent 13.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.</p>
		<p>Green?</p> <p>Agent 14.: Where several first/given names are indicated, they should preferably be separated by a comma. Please verify.</p>
13-2-6	Validation messages Contents	<p>Yellow!</p> <p>The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.</p>
13-2-8	Validation messages Payment	<p>Green?</p> <p>Please ensure that you have a valid deposit account with the receiving Office selected.</p>

PCT/US 00/30294

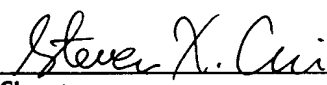
DOCKET OR REFERENCE NUMBER: P1735R1

EXPRESS MAIL LABEL: EL141796391US  
MAILED: 02 November 2000

CERTIFICATE RE: SEQUENCE LISTING

Inventors: Ben-Quan Shen; Thomas Zioncheck  
Applicant: GENENTECH, INC., et al.  
Title: Modulation of eNOS Activity and Therapeutic Uses Thereof

I hereby state that the Sequence Listing submitted herewith is submitted in paper copy and a computer-readable diskette, and that the information recorded in computer readable form is identical to the written sequence listing. I further state that this submission includes no new matter.

Steven X. Cui	44,637
Name of Registered Representative	Reg. No.
	02 November 2000
Signature	Date